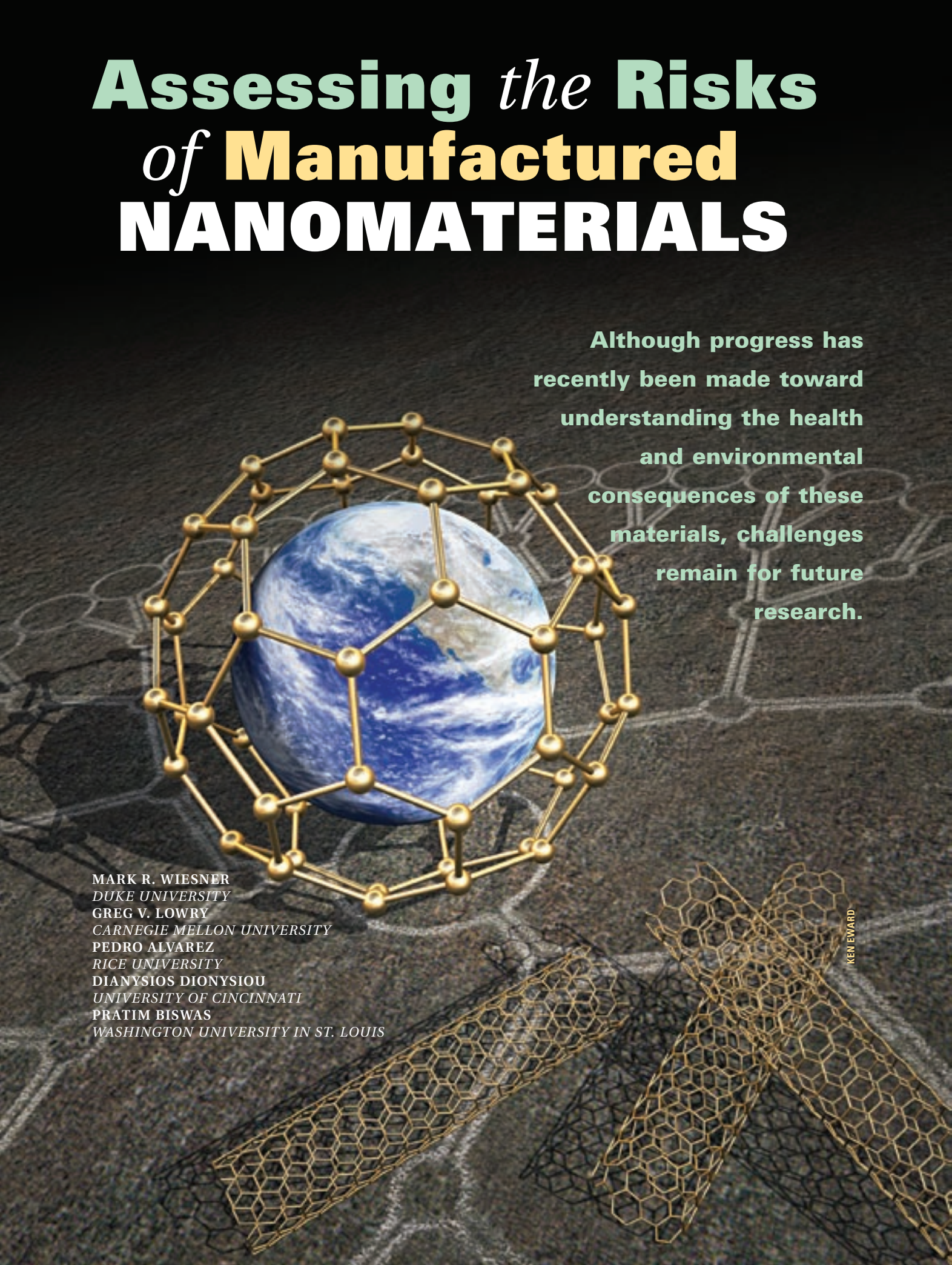


Assessing *the* Risks of **Manufactured** **NANOMATERIALS**

Although progress has recently been made toward understanding the health and environmental consequences of these materials, challenges remain for future research.

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In the evolution of nanotechnology, manufactured nanomaterials are an important step toward a long-term vision of building objects atom-by-atom and molecule-by-molecule with processes such as self-assembly or molecular assemblers (1, 2). Innovations in analytical and imaging technologies first paved the way for perceiving, measuring, and manipulating nanoscale objects, typically defined as those having a characteristic dimension <100 nm. The ability to design materials at the nanoscale is now leading to the rapid development of an industry that provides nanomaterials for a range of industrial and consumer products. Commercial applications of nanomaterials currently available or soon to appear include nanoengineered

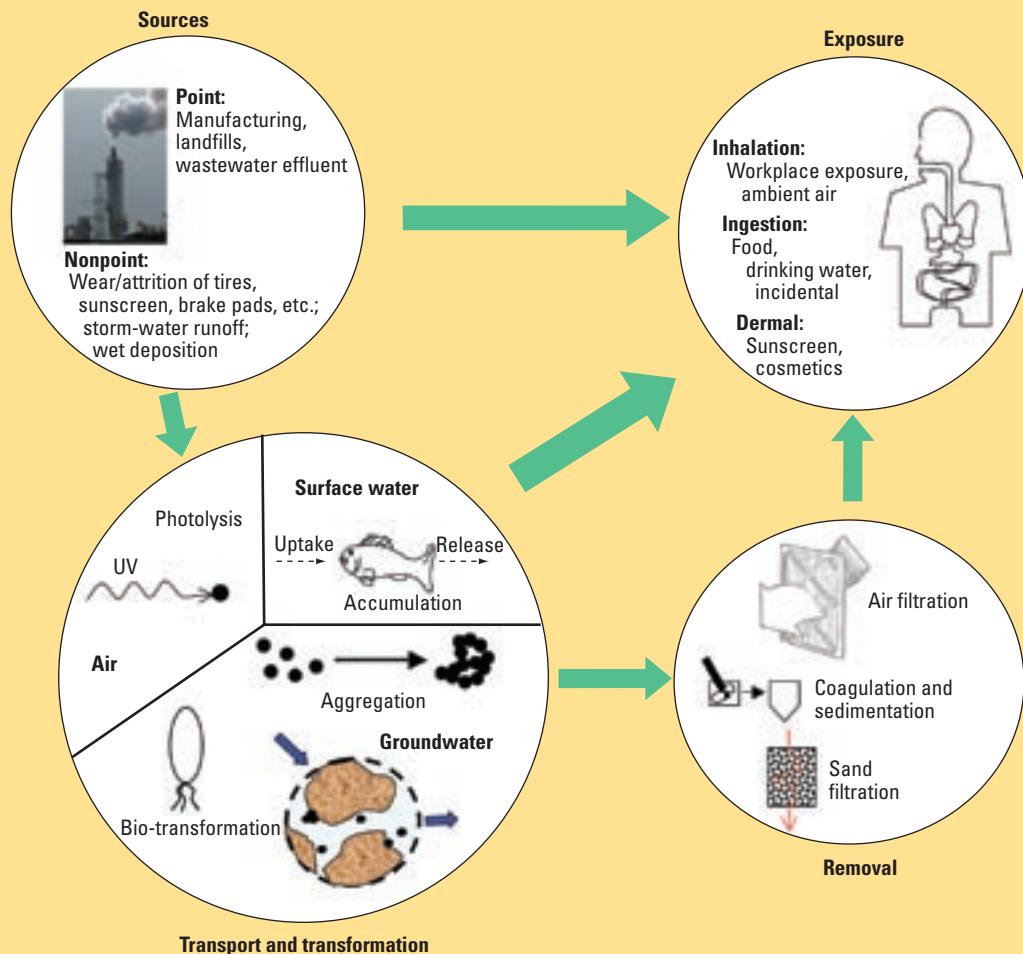
titanium particles for sunscreens and paints; fullerene nanotube composites in tires, tennis rackets, and video screens; fullerene cages in cosmetics; silica nanoparticles as solid lubricants; metal nanoparticles for groundwater remediation; and protein-based nanomaterials in soaps, shampoos, and detergents. In the environmental technology industry alone, nanotechnologies hold great promise for reducing the production of wastes, using resources more sparingly, cleaning up industrial contamination, providing potable water, and improving the efficiency of energy production and use.

The production, use, and disposal of nanomaterials will inevitably lead to their appearance in air, water, soils, or organisms (Figure 1). The environmen-

FIGURE 1

Nanomaterial releases to the environment

Releases may come from point sources, such as factories or landfills, and from nonpoint sources, such as wet deposition from the atmosphere, storm-water runoff, and attrition from products containing nanomaterials. Biochemical cycling of nanomaterials may involve photochemical reactions in the atmosphere; aggregation; or uptake, accumulation, transformation, and degradation in organisms. Long-range atmospheric transport, as well as transport in saturated and unsaturated regions in the subsurface, are possible. Nanomaterials in groundwater and surface water used for drinking water will be subject to conventional treatment methods, such as flocculation, sedimentation, and sand or membrane filtration. Air filters and respirators will be used to remove nanomaterials from air. Human exposure to nanomaterials is most likely during nanomaterial manufacturing, but inhalation of nanomaterials released to the atmosphere and ingestion of drinking water or food (e.g., fish) that have accumulated nanoparticles may also be possible. Dermal exposure from sunscreens and cosmetics is also likely.



tal and health consequences of these materials, their production, and the life-cycle implications of the products merit attention now, during the early stages of development. The largely unknown risks to human health and ecosystems presented by nanomaterials have been the subject of considerable speculation. Recent research has focused largely



on the possible toxicity of these materials. However, whether a substance is dangerous involves determining not only its potential hazards, such as toxicity, but also to what degree the material will ever come into contact with a living cell. Although some time may pass before the risks of nanomaterials can be accurately assessed, an urgent need exists to consider the possible impacts of nanomaterial fabrication and the manner in which conventional chemical feedstocks and wastes will be handled.

The U.S. National Nanotechnology Initiative (NNI), which includes several government agencies (e.g., the U.S. EPA, the National Science Foundation, the National Institutes of Health), supports research programs to investigate the fate, transport, and life cycle of nanoparticles in the environment and their potential toxicity to humans and the environment. In fiscal year 2004 (FY '04), 3–5% of NNI's \$849 million budget was targeted to research on nanoscale processes in the environment, as well as the environmental and social implications of nanotechnologies. Environment and health issues are also a specific area for research in the FY '05 NNI budget. The Woodrow Wilson International Center for Scholars estimates that out of a current budget of >\$1 billion for nanotechnology research under the NNI, \$39 million is earmarked for environmental, health, and safety studies. Movement has also taken place toward including environmental and health issues in the EU and Japanese research budgets for nanotechnology. The current European budget for research in these areas is ~\$7.5 million, a much smaller share of their total nanotechnology research budget than in the U.S.

Looking for answers to questions on environmental impacts of nanotechnology in the early stages of development may result in better and safer products and less long-term liability for industry. Indeed, due diligence is the standard demanded by the law, if not the public. Research on health and environmental impacts of nanotechnology follows both the precautionary approach to policy often favored in Western Europe (no data, no market) and the risk-based approach to formulating policy that is more frequently used in the U.S. (no data, no regulation). Although the constituencies in each instance may differ, both approaches make a case for reliable data. In this article, we summarize recent progress made toward providing the data required to assess some of the environmental consequences of an emerging nanomaterials industry.

Nanomaterials production

The methods for producing nanoparticles are as varied as the materials themselves. For example, fullerenes comprise a class of nanomaterials that are made of a newly discovered allotrope of carbon and exist as hollow spheres, ellipsoids, or tubes. They have created significant commercial interest because of their high strength, electrical conductivity, electron affinity, structure, and versatility. Some fullerenes have been found naturally as combustion products. As a result, they are typically fabricated by chemical vapor deposition, arc discharge, or controlled pyrolysis. The formation of nanotubes typically requires a metal catalyst, such as iron or nickel (3), to organize carbon presented as CO, whereas spherical "buckyballs" can be formed by burning benzene in an oxygen–argon flame with careful control of gas flow (4).

Quantum dots (QDs) are semiconductors that display narrow fluorescence or absorption bands because of quantum constraints imposed on electrons by the finite size of the material. Applications of QDs include medical imaging and sensors. QDs such as ZnSe can be made from microemulsions by a self-assembly procedure: The metal is introduced to the organic phase (e.g., heptane) and used to subsequently form a microemulsion, which is then activated to generate particle formation at the droplet surface (5).

In contrast with these bottom-up methods for nanoparticle fabrication, metal oxanes (e.g., alumoxane) are made in a top-down procedure in which a mineral (boehmite in the case of alumoxanes) is cut into smaller pieces by an organic acid in an aqueous solution (6). Metal oxanes have been used as alternatives to sol–gel precursors for membrane fabrication and thin films.

TiO₂ nanoparticles are widely used for applications such as photocatalysts, pigments, and cosmetic additives. Many procedures have been reported for producing TiO₂ nanoparticles; most typically involve synthesis by hydrolysis and calcination (7). Flame and furnace reactor syntheses, in which powders such as TiO₂ and SiO₂ are produced by combusting vaporizable compounds (e.g., TiCl₄), appear to be the most commercially successful approach to gas-phase synthesis of nanoparticles (8). The sol-gel method (liquid-phase synthesis)—formation of solid inorganic materials from molecular precursors via room-temperature, wet-chemistry-based procedures—is easily adapted to making powders as well as films. This method typically yields amorphous TiO₂, and a subsequent calcination step is usually required to crystallize the material. Other common approaches include the hydrothermal and the furnace pyrolysis methods.

Zerovalent iron nanoparticles (nanoferron) are relatively advanced environmental nanotechnologies in terms of large-scale commercial production. They have been used at >20 sites for the in situ remediation of amenable groundwater contaminants in pilot- or full-scale operations. Nanoferron is produced commercially by several companies; each uses a proprietary synthesis method. In general, two na-

noiron synthesis methods are used commercially: the bottom-up and the top-down approaches. The bottom-up approach begins with dissolved iron in solution and uses a reductant to convert dissolved metal to nanoparticulate Fe⁰ (9, 10). The resulting particles may be amorphous or polycrystalline Fe⁰ (11–13) or may consist of a magnetite shell around an Fe⁰ core (11, 12, 14). This shell provides more favorable properties, such as a longer lifetime in water. The top-down approach begins with micrometer- to millimeter-sized iron filings, which are ball-milled to fine, nanosized particles.

Elements of risk

Responsible uses of manufactured nanomaterials in commercial products and environmental applications, as well as prudent management of the associated risks, require a better understanding of their mobility, bioavailability, and impacts on a wide variety of organisms. For nanomaterials to present a risk, there must be both a potential for exposure and a hazard, such as toxicity, that results after exposure. Exposure varies on the basis of conditions such as the manner in which materials are handled in the workplace, how nanomaterials partition to various phases (e.g., water and air), the mobility of nanomaterials in each of these phases, their persistence, and the magnitude of the sources (e.g., size of markets). Research evaluating potential worker exposure to nanomaterials in fabrication facilities has focused largely on airborne pathways (15) and, to a lesser degree, on direct dermal exposure (16). The transport and fate of nanomaterials in aquatic environments has received relatively little attention.

Similarly, recent evaluations of the hazards associated with nanomaterials have focused mainly on damage to lung tissue after inhalation. The earliest work on toxicity was performed in connection with studies for the possible use of nanomaterials in tumor treatment, drug delivery, and medical imaging. More recent work has begun to consider the impacts of nanomaterials on bacteria and aquatic life. Although some nanomaterials, such as fullerenes, may have very low solubilities in water, functionalization may increase their affinity for the aqueous phase and their potential reactivity with cells. Indeed, increasing nanoparticle affinity for the aqueous phase may be a requirement for uses of these materials in applications ranging from drug delivery to groundwater remediation. For example, hydroxylation of fullerenes, either intentionally or in the fabrication process, will increase their apparent solubility. Chemical or biological oxidation may add, remove, or modify functionalities associated with mineral nanoparticles, and the adsorption of natural organic matter may alter their charge and stability in suspension.

Nanomaterials hazards

Cellular interactions and toxicity. Numerous studies have investigated the human health implications of nanomaterials (Table 1). Only recently have researchers begun to study the potential ecological risks and impacts of nanomaterial releases to the environment. To date, how much exposure to “nanoliter” may affect living organisms remains unknown, as do any specific mechanisms of toxicity.

Oberdörster published an early study that pointed to possible negative impacts of nanomaterials on

TABLE 1

Cytotoxicity studies of selected nanomaterials

Nanomaterial	Effects observed	References
<i>Fullerene</i>		
C ₆₀ water suspension	Antibacterial; cytotoxic to human cell lines; taken up by human keratinocytes; stabilizes proteins	17, 18
C ₆₀ encapsulated in poly(vinylpyrrolidone), cyclodextrins, or poly(ethylene glycol)	Damages eukaryotic cell lines; antibacterial	19, 20
Hydroxylated fullerene	Oxidative eukaryotic cell damage	20
Carboxyfullerene (malonic acid derivatives)	Bactericidal for Gram-positive bacteria; cytotoxic to human cell lines	21, 22
Fullerene derivatives with pyrrolidine groups	Antibacterial; inhibits cancer cell proliferation; cleave plasmid DNA	23
Other alkane derivatives of C ₆₀	Antimutagenic; cytotoxic; induces DNA damage in plasmids; inhibits protein folding; antibacterial; accumulates in rats' livers	24, 25
Metallofullerene	Accumulates in rats' livers	26
<i>Inorganic</i>		
Silicon dioxide (SiO ₂)	Pulmonary inflammation in rats	27
Anatase (TiO ₂)	Antibacterial; pulmonary inflammation in rodents	28, 29
Zinc oxide (ZnO)	Antibacterial (micrometer scale); pulmonary effects in animals and humans	30, 31

the health of aquatic organisms (32). This pioneering study concluded that stable colloidal suspensions of buckminsterfullerenes (C_{60}) in water (nC_{60}) exerted oxidative stress and caused severe lipid peroxidation in fish brain tissue. Whether oxidative stress was the result of reactive oxygen species (ROS) produced by nC_{60} or by the cellular immune response system was not investigated. The cytotoxicity of other water-soluble, photosensitive fullerenes (e.g., carboxylated C_{60} , fullerene[60]pyrrolidine) and inorganic nanomaterials (e.g., SiO_2 , TiO_2 , ZnO) has also been associated with oxidative stress, on the basis that light stimulation causes ROS production, and this leads to high toxicity (33, 34).

On the other hand, numerous observations have been made of fullerenes acting as antioxidants. Indeed, the antioxidant properties of C_{60} have been compared to those of vitamins C and E in preventing lipid peroxidation induced by superoxide and hydroxyl radicals (35). This apparent dichotomy underscores the need for research on nanomaterial-cell interactions and the resulting effects on metabolic processes and cell physiology as a function of dose and exposure conditions.

Microbial ecotoxicology is a particularly important consideration in elucidating cytotoxicity mechanisms that could be extrapolated to eukaryotic cells. Moreover, because microorganisms are the foundation of all known ecosystems, serving as the basis of food webs and the primary agents for global biogeochemical cycles, they are important components of soil health. Microorganisms could serve as potential mediators of nanoparticle transformations that affect their mobility and toxicity. Thus, a better understanding of nanomaterial-microbe interactions is important because it will ensure that nanotechnology evolves as a tool to improve material and social conditions without exceeding the ecological capabilities that support them.

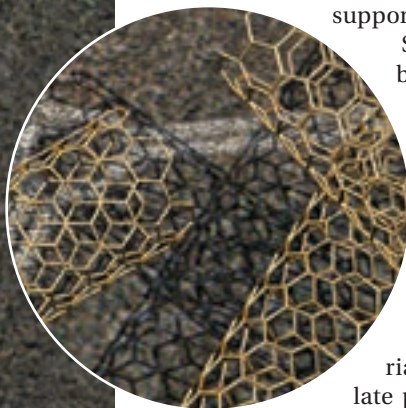
Suspensions of nC_{60} have been reported to exhibit antibacterial activity, although the possible mechanisms responsible for such toxicity remain unknown (17, 19, 21, 22, 36). Unlike some eukaryotic cells that can assimilate large nanoparticles (up to 100 nm) (37), bacteria generally cannot assimilate particles >5 nm, including nC_{60} (38). Thus, antibacterial activity likely involves direct contact of nanoparticles with the cellular surface; this suggests that the surface chemistry and morphology of nanomaterials could be very influential factors in their toxicity. The antibacterial effect of nC_{60} could also be due to oxidative stress. Some oxidation reactions damage the cell membrane and affect cell permeability and fluidity, leaving cells more susceptible to osmotic stress or hindering nutrient uptake. Furthermore, bacterial membranes are the loci of electron transport

phosphorylation and energy transduction, which can be disrupted if a redox-sensitive nanomaterial contacts membrane-bound electron carriers and withdraws electrons from the transport chain. In theory, such redox interactions could also generate free radicals that oxidize double bonds on fatty-acid tails of membrane phospholipids; this could result in the formation of highly reactive epoxides that can further compromise the integrity of the cell membrane and even damage DNA. However, whether nanomaterials cause oxidative stress by generating ROS or by the cell's response to the nanoparticles is not yet clear.

These theoretical interactions could serve as a guide for advanced microscopic and chemical analyses of cell constituents to elucidate toxicity mechanisms and discern physiological characteristics that confer bacterial resistance to toxicity. For example, it is plausible that cells possessing a high concentration of antioxidants (e.g., reduced glutathione) or enzymes that destroy ROS (e.g., catalase, peroxidase, superoxide dismutase) might be less susceptible to nanomaterial toxicity. Theoretical considerations also suggest that smaller nanoparticles are likely to be more toxic because of their large specific surface areas, which are conducive to greater bioavailability. Thus, factors that promote coagulation and precipitation of nanoparticles in the environment, such as increases in salt concentration, are likely to mitigate ecotoxicity. It has been suggested that derivatization of fullerenes decreases toxicity (18). However, derivatization provokes numerous changes in the physical characteristics of these materials, including aggregation state, hydrophobicity, and reactivity, that have not been controlled in studies to date.

Metal and metal-oxide nanoparticles (e.g., nanoiron, magnetite, TiO_2) have been proposed for groundwater remediation (11, 39, 40), water treatment (41, 42), and removal of toxic contaminants from air streams (43). Their widespread use could expose biological systems through inhalation, dermal contact, or ingestion and absorption through the digestive tract. A recent investigation indicates that CeO_2 nanoparticles are taken up into human fibroblasts in vitro (44). However, few other studies describe the effects of particles once they are taken up into the cells.

Preliminary investigations of the in vitro response of central nervous system (CNS) microglia to low concentrations of nanoiron (2–30 ppm) and nanomagnetite (2–30 ppm) indicate that these nanoparticles produce an oxidative stress response and are taken up into cells (Figure 2). Noncytotoxic doses of Degussa P25 nano- TiO_2 caused rapid and sustained release of ROS by CNS microglia, indicating the potential for neurotoxicity. Exposure to these nanoparticles also affected ATP levels, caused mitochondrial depolarization, and stimulated an oxidative burst in the microglia and neurons. These results suggest the potential for negative health effects from exposure and uptake of nanoparticles into mammalian cells. However, it is important to note that these are in vitro responses and represent significantly higher exposures than expected. Tox-



icity data and the potential exposure levels must be considered simultaneously to determine the risks.

Transport and fate of nanoparticles. The higher mobility of nanomaterials in the environment implies a greater potential for exposure as they are dispersed over greater distances and their effective persistence in the environment increases. One phenomenon that may reduce exposure is the propensity of nanoparticles to attach to surfaces or to form

involves attachment between mobile sites. The physics of particle transport, which involves well-defined geometries, such as spherical particles depositing in packed beds of spheres, is relatively well understood and compares very well with measurements. However, models of the transport of particles with more complex surfaces, such as porous fractal aggregates, require simplifying assumptions. Nonetheless, the fluid mechanics of nanoparticle transport does not appear to require the introduction of new, previously unconsidered factors.

In contrast, our ability to resolve observations of particle attachment as particles approach and contact surfaces with those calculated from models for even relatively idealized systems is still limited. The attachment efficiency, α , is a function of numerous phenomena, including van der Waals forces, electrical double-layer interactions, steric interactions, hydration forces, and particle and surface hydrophobicity. The value of α is 1 when no barriers to particle attachment exist, but it may exceed 1 if phenomena at small separation distances draw particles to the attachment surface.

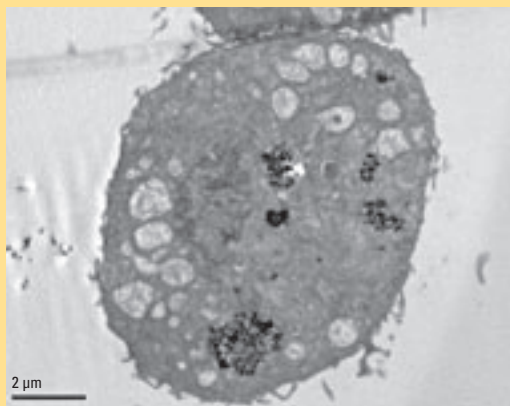
In the case of very small (<2-nm) nanoparticles, the simplifying assumptions commonly applied in theoretical considerations of particle attachment may no longer hold. For example, structural or hydration forces, diffuse-layer interactions, and steric interactions that affect particle stability may be important over length scales that are large in comparison with some nanoparticle dimensions. Extensions or modifications of current theory may be needed to describe α for some smaller nanomaterials. Despite the existence of numerous publications describing procedures for producing nanoparticles of specific sizes, shapes, and compositions, little theoretical consideration has been given to the special properties of nanoparticles that might affect their potential for aggregation (46) and little evaluation has been done of the transport properties of these new materials in aqueous systems. For these reasons, experimental quantification of nanoparticle mobility on the basis of particle transport and attachment as they affect deposition and aggregation is necessarily empirical at this time.

Deposition and mobility in porous media. Initial work on nanomaterial mobility in formations that resemble groundwater aquifers or sand filters has shown that one type of nanomaterial (e.g., fullerol) may be very mobile, but a second form (e.g., nC_{60}) may stay put (47). Differences in nanoparticle mobility in porous media appear to be a function of both surface chemistry and particle size. Although these results underscore the need to avoid generalizations of nanoparticle risks on the basis of differences in potential exposure, they also suggest that even the most mobile of these materials are likely to be removed in filters during water treatment. Thus, the evidence does not support the scenario of a new nanoparticulate contaminant that current water-treatment infrastructure cannot handle. Conditions such as high ionic strength and the presence of even small quantities of divalent ions tend to increase retention of nanoparticles by porous media (48).

FIGURE 2

Transmission electron microscope image showing uptake of nanoiron into microglia cells

The cells were exposed to 2 mg/L nanoiron for 18 h. The cells were then frozen and cut into thin sections for analysis. Light-colored circles are cell mitochondria; black areas are nanoiron that has been assimilated into the cell.



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aggregates. For example, particles that are readily transported and attach to mineral surfaces may be less mobile in porous media, such as groundwater aquifers or the sand filters used in potable-water treatment. Intuitively, the assumption is often made that nanoparticles will be highly mobile in porous media because of their small size. However, all other factors being equal, smaller particles should not be very mobile because their relatively large diffusivity produces more frequent contacts with the surfaces of aquifer porous media. Similar considerations lead to a high deposition rate of ultrafine airborne particles in the lungs.

Particle deposition and aggregation are closely related phenomena. Factors that favor particle removal by deposition frequently tend to favor aggregation and subsequent removal by settling. Deposition and aggregation can be described as a two-step process of particle transport followed by attachment. For example, particle deposition in an aquifer can be described as a sequence of particle transport to the immobile surface or aquifer material "collector", followed by attachment to the collector (45). Deposition and aggregation differ in the sense that particle deposition involves attachment to an immobile site, whereas particle aggregation

Because groundwater aquifers and surface waters typically have ionic strengths of $>10^{-4}$ M and significant concentrations of calcium or magnesium, conditions should favor nanomaterial deposition.

Some applications of nanoparticles may involve their intentional release to the environment. For example, in situ groundwater remediation with reactive nanoparticles will likely become a useful remediation tool (49, 50). To effectively deliver nanoiron, unique surface coatings will be required to make the particles mobile in the subsurface (51);

these modifications may in turn increase their potential for unwanted exposure to humans and other

organisms. Many other types of nanomaterials will also require surface coatings for their intended application (e.g., metal-oxide nanoparticles, QDs used as magnetic resonance imaging contrast agents) (52).

The three classes of typical surface coatings are polymers, polyelectrolytes, and surfactants. These coatings can impart

charge to the particles (positive or negative) and can stabilize them against aggregation and deposition. Coatings can also affect bactericidal properties. For example, several studies have observed toxic effects from positively charged nanoparticles, but these effects are not seen when the same particles are coated with negatively charged functional groups. The efficacy of the treatment systems that remove small particles from water (e.g., flocculation and sedimentation, or sand filtration) may also decrease as the result of such surface coatings. Understanding the effects of surface chemistry on the fate of nanoparticles in the environment is imperative to designing coatings that maximize their effectiveness while minimizing any negative ecological consequences. Indeed, applications of nanoparticles that involve their direct introduction to the environment promise to be contentious until the uncertainties regarding fate, transport, and toxicity are addressed.

Aggregation. Although many nanomaterials are produced with a targeted size that may be quite small, these particles frequently form much larger colloidal aggregates. For example, 20-nm anatase particles, such as those used in column experiments to explore nanomaterial deposition, form aggregates with a narrow size distribution and stable diameter of ~ 200 nm. Similarly, hydroxylated C_{60} (fullerol) forms stable aggregates ~ 100 nm in diam in pure water. When even small amounts of salts are added, these and other nanomaterials readily form large settleable aggregates (48). Although the low solubility of fullerenes leads to a hydrophobic clumping in water, a strong attractive force may also exist between fullerenes. Hamaker constants of $50\text{--}60 \times 10^{-20}$ J are reported for carbon nanotubes

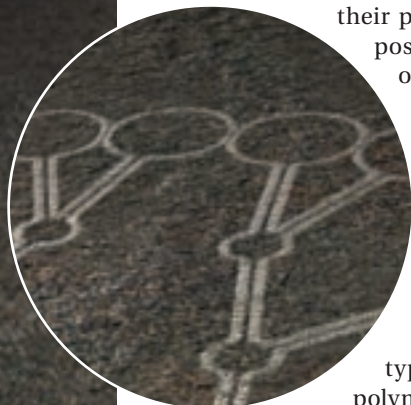
(53), comparable to the 47×10^{-20} J commonly used for graphite. Given that these values are relatively high, it is not surprising that carbon nanotubes form aggregates of much larger dimensions than the individual nanoparticles. Several approaches have been reported for producing aqueous suspensions of nC_{60} $\sim 20\text{--}200$ nm in diam without stabilizing agents or apparent functionalization (54–58). The structure and charge characteristics of the nC_{60} aggregates have been found to vary considerably as a function of the method used to produce them (59). For nanoiron, magnetic attractive forces between particles result in rapid aggregation at low volume fractions.

Some evidence suggests that the deleterious effects on bacterial populations are greater for smaller aggregates of C_{60} than for larger ones. Thus, aggregation of nanoparticles may mitigate both exposure and toxicity in some cases.

Redox transformations. These reactions are very important for the degradation of organic compounds. Redox processes are also the basis of various precipitation and dissolution reactions that influence the sequestration and mobility of inorganic metals. Thus, redox reactions might be important for the transformation and fate of engineered nanoparticles.

Redox reactions are often mediated by microorganisms, either directly through enzymatic activity or indirectly through the production of biogenic oxidants (e.g., ROS produced by lignocellulolytic fungi) or reductants (e.g., surface-associated Fe(II), a common abiotic reductant in natural systems that can be produced by iron-reducing bacteria). Whether nanomaterials could be transformed to an appreciable extent by such abiotic redox processes in the environment is unknown and would likely depend on the thermodynamic feasibility and kinetic facility of the electron transfer.

To date, no systematic evaluations of fullerene transformation via biochemical mechanisms have been recorded. However, extensive literature exists on organisms such as lignocellulolytic fungi that possess nonspecific extracellular biocatalytic capabilities to degrade recalcitrant organics. Furthermore, numerous citations document the chemical reactivity of fullerenes (oxidation and reduction reactions) (25, 60–70) and confirm fullerene oxidation via chemically based model enzyme systems (71). Specifically, Fenton's chemistry— $H_2O_2 + Fe(II)$ generating hydroxyl radicals—is considered to be a chemical model for hydroxylation of carbon atoms mediated by fungal enzymes, such as cytochrome P450, peroxidases, and laccases. Thus, fullerenes could plausibly be oxidized (e.g., hydroxylated) by such exocellular fungal enzymes with relaxed specificity. Furthermore, the antioxidant properties of fullerenes and their high propensity to accept electrons suggest that microbe-produced reductants (e.g., reduced glutathione and cobalamin) might also transform fullerenes. Investigating whether such fullerene biotransformations could occur, and their resulting effect(s) on toxicity, could be a fruit-



ful avenue of research, not only to evaluate this important natural attenuation mechanism, but also to assess the stability and biodeterioration potential of fullerenes.

Workplace exposure. Large concentrations of nanoparticles may be present in occupational environments, which deserve particular attention from the standpoint of exposure. Limited data and guidelines are available for handling nanoparticles in occupational settings as well as research laboratories. For example, guidelines for the selection of respiratory protection for specific types of nanoparticles are lacking. However, much can be learned from studies of worker exposure to nanoscale particles produced unintentionally in occupational environments (8, 72). For example, studies that have focused on the formation and growth dynamics of nanoscale particles from welding processes have been used recently to design methodologies for reducing concentrations of particles in welding booths (73) (Figure 3).

FIGURE 3

Studies on the unintentional formation of nanoscale particles in processes such as welding can be used to develop strategies to minimize exposure

Changes in ventilation patterns in the welding booth have demonstrated a suppression of the nanoparticle concentrations in the vicinity of the welder.



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The comparison is particularly appropriate because many processes for creating engineered nanoparticles occur by nucleation of particles in high-temperature, gas-phase processes similar to the conditions present in welding. Gas-phase routes are readily scalable for production of larger quantities of nanomaterials, and in many instances they allow for the strict control of size and other characteristics.

Exposure to nanoparticles can occur through the skin, lungs, and the gastrointestinal tract. A com-

plex mix of compounds in the gastrointestinal tract can interact with particles and reduce the adverse effects of ingested micrometer-sized toxins. Similar processes may apply to engineered nanoparticles. The most critical concern over health and environmental effects occurs when nanoparticles are aerosolized. Aerosolized nanoparticles are highly mobile and can enter the human body via inhalation. Although defense mechanisms exist, alveolar tissue is not as well protected as the skin and gastrointestinal tract against environmental insults.

Hypotheses about the physicochemical characteristics of particles responsible for possible adverse health effects have considered general properties, such as surface area or size, acidity, and metal content. Although regulations are often written in terms of mass concentrations, particle number and surface area may be more relevant than mass concentration for determining toxicity. In air, nanoscale particles have been found to act synergistically with other pollutants, such as O₃ or NO_x (74). The complex interactions between particles and gaseous components complicate the assessment of the nanoparticle effects and their associated risks.

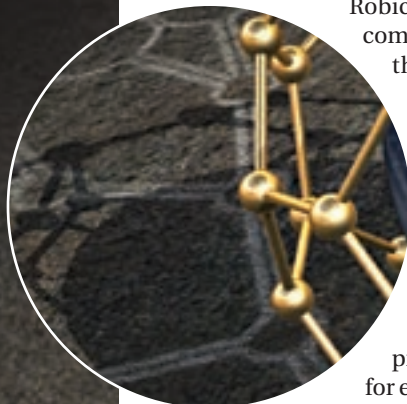
While approaches to safe nanotechnology are being developed (72), methods for characterizing and quantifying nanoparticles in occupational environments remain largely undeveloped. All potential sources of emission need to be identified, including those available during production, handling, and use. Control technologies should be developed to ensure that emissions are minimized. Respiratory deposition of nanoparticles needs to be understood better, and the interactions with other constituents that can impact health should be explored.

Responsible production of nanomaterials

Definitive answers on the risks posed by nanomaterials are perhaps years away and, in any event, are likely to emerge on a case-by-case basis. By comparison, growth in the nanomaterials industry is occurring rapidly. Some organizations (e.g., the National Science Foundation, the Nano Business Alliance) have estimated that, with forecast annual growth rates of 20–40%, the value of nanotechnology markets will rise to >\$1 trillion by 2010. A critical challenge for the emerging nanomaterials industry is to ensure that the potential health and environmental impacts of nanomaterial fabrication are small. Although the rapid developments in these industries imply a short window of opportunity, even small adjustments to their early trajectories may produce large returns in terms of reduced impacts on human health and the environment.

Although many unknowns surround the fate of nanomaterials in the environment and their impacts, a great deal is known about the properties and effects of the materials used to produce them. For example, benzene is a feedstock in C₆₀ production (4), CO is used to produce single-walled carbon nanotubes (3), and heavy metals are a component of QDs (5). Materials such as these require special handling to protect workers and avoid contamination or other legacy issues. As an instructive compari-

son, growth in the semiconductor industry created a series of groundwater contamination issues arising from the use of solvents and heavy metals. The toxicity of computer chips may not have been an issue, but the toxic materials used to make the chips presented important environmental risks. It is therefore appropriate to consider the risks of fabrication well before information on the risks of nanomaterials is available.



Robichaud et al. performed a comparative risk assessment for the fabrication of nanomaterials that excluded any impacts or risks presented by the nanomaterials themselves (75). A representative synthesis method was selected for each nanomaterial on the basis of its potential for scale-up. A list of feedstocks, products, and waste streams for each fabrication step was developed, and the physicochemical properties and the inventoried material quantities were used to assess relative risk related to factors such as volatility, carcinogenicity, flammability, toxicity, and persistence. These factors were combined via an actuarial protocol developed by the insurance industry to calculate premiums for chemical manufacturers. Results from this analysis determined that the relative environmental risks from manufacturing five varieties of nanomaterials were comparable to or less than those from other common industrial manufacturing processes. Among the needs for future work in these areas are refined estimates of the size of prospective industries, incorporation of the risks of the nanomaterials, and a life-cycle assessment of products that incorporate these materials.

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